



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
|---|--|---|---|
| (51) International Patent Classification ⁶ : C07D 277/42, A61K 31/425, C07D 417/12, A61K 31/44, C07D 277/56, 417/06, 417/14, A61K 31/47, 31/50 | | A3 | (11) International Publication Number: WO 99/21845 |
| | | | (43) International Publication Date: 6 May 1999 (06.05.99) |
| (21) International Application Number: PCT/US98/22809 | | Diego, CA 92122 (US). XIAO, Wei [CN/US]; 4043 Carmel Springs Way, San Diego, CA 92130 (US). YANG, Yi [CN/US]; 8976 Gainsborough Avenue, San Diego, CA 92129 (US). | |
| (22) International Filing Date: 27 October 1998 (27.10.98) | | | |
| (30) Priority Data: 60/063,634 27 October 1997 (27.10.97) US 60/063,666 28 October 1997 (28.10.97) US | | | |
| (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US Not furnished (CIP) Filed on Not furnished | | | |
| (71) Applicant (for all designated States except US): AGOURON PHARMACEUTICALS, INC. [US/US]; 10350 North Torrey Pines Road, La Jolla, CA 92037 (US). | | (74) Agents: EVANS, Linda, S. et al.; Agouron Pharmaceuticals, Inc., 10350 North Torrey Pines Road, La Jolla, CA 92037 (US). | |
| (72) Inventors; and (75) Inventors/Applicants (for US only): CHONG, Wesley, K., M. [US/US]; 134 Honeycomb Court, Encinitas, CA 92024 (US). CHU, Shao, Song [CN/US]; 1604 Jerrilynn Place, Encinitas, CA 92024 (US). DUVADIE, Rohit, R. [NP/US]; 10320 Maya Linda Road #A-316, San Diego, CA 92024 (US). LI, Lin [CN/US]; 3950 Mahaila Avenue #J-36, San | | (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). | |
| | | Published With international search report. | |
| | | (88) Date of publication of the international search report: 19 August 1999 (19.08.99) | |
| (54) Title: 4-AMINOTHIAZOLE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS INHIBITORS OF CYCLIN-DEPENDENT KINASES | | | |
| <div style="text-align: center;"> <p>(I)</p> </div> | | | |
| (57) Abstract | | | |
| <p>This invention is directed to aminothiazole compounds of formula (I) wherein R¹ is a substituted or unsubstituted group selected from: C₁₋₆-alkyl; C₁₋₆-alkenyl; C₁₋₆-alkynyl; C₁₋₆-alkoxyl; C₁₋₆-alcohol; carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic, cycloalkyl; carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic, aryl; carbonyl; ether; (C₁₋₆-alkyl)-carbonyl; (C₁₋₆-alkyl)-aryl; (C₁₋₆-alkyl)-cycloalkyl; (C₁₋₆-alkyl)-(C₁₋₆-alkoxyl); aryl-(C₁₋₆-alkoxyl); thioether; thiol; and sulfonyl; wherein when R¹ is substituted, each substituent independently is a halogen; haloalkyl; C₁₋₆-alkyl; C₁₋₆-alkenyl; C₁₋₆-alkynyl; hydroxyl; C₁₋₆-alkoxyl; amino; nitro; thiol; thioether; imine; cyano; amido; phosphonato; phosphine; carboxyl; thiocarbonyl; sulfonyl; sulfonamide; ketone; aldehyde; ester; oxygen; carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic, cycloalkyl; or carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic, aryl; and R² is a carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic, ring structure having a substituent at the position adjacent to the point of attachment, which ring structure is optionally further substituted, where each substituent of R² independently is a halogen; haloalkyl; C₁₋₆-alkyl; C₁₋₆-alkenyl; C₁₋₆-alkynyl; hydroxyl; C₁₋₆-alkoxyl; amino; nitro; thiol; thioether; imine; cyano; amido; phosphonato; phosphine; carboxyl; thiocarbonyl; sulfonyl; sulfonamide; ketone; aldehyde; ester; oxygen; carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic, cycloalkyl; or carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic, aryl; or a pharmaceutically acceptable salt of a compound of formula (I), or a prodrug or pharmaceutically active metabolite of a compound of formula (I) or pharmaceutically acceptable salt thereof, for inhibiting cyclin-dependent kinases (CDKs), such as CDK1, CDK2, CDK4, and CDK6. The invention is also directed to the therapeutic or prophylactic use of pharmaceutical compositions containing such compounds and to methods of treating malignancies and other disorders by administering effective amounts of such compounds.</p> | | | |

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|----|--------------------------|----|--|----|--|----|--------------------------|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | ML | Mali | TR | Turkey |
| BG | Bulgaria | HU | Hungary | MN | Mongolia | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MR | Mauritania | UA | Ukraine |
| BR | Brazil | IL | Israel | MW | Malawi | UG | Uganda |
| BY | Belarus | IS | Iceland | MX | Mexico | US | United States of America |
| CA | Canada | IT | Italy | NE | Niger | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NL | Netherlands | VN | Viet Nam |
| CG | Congo | KE | Kenya | NO | Norway | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NZ | New Zealand | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | PL | Poland | | |
| CM | Cameroon | KR | Republic of Korea | PT | Portugal | | |
| CN | China | KZ | Kazakstan | RO | Romania | | |
| CU | Cuba | LC | Saint Lucia | RU | Russian Federation | | |
| CZ | Czech Republic | LI | Liechtenstein | SD | Sudan | | |
| DE | Germany | LK | Sri Lanka | SE | Sweden | | |
| DK | Denmark | LR | Liberia | SG | Singapore | | |
| EE | Estonia | | | | | | |

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/22809

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D277/42 A61K31/425 C07D417/12 A61K31/44 C07D277/56
C07D417/06 C07D417/14 A61K31/47 A61K31/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| Y | WO 92 20642 A (RHONE-POULENC RORER INTERNATIONAL (HOLDINGS) INC.) 26 November 1992 see claims 1-4,7 --- | 1-14,16, 17 |
| Y | WO 95 15758 A (RHONE-POULENC RORER PHARMACEUTICALS INC.) 15 June 1995 see claims 1-3,6,7 --- | 1-14,16, 17 |
| Y | WO 96 39145 A (RHONE-POULENC RORER PHARMACEUTICALS INC.) 12 December 1996 see claims 1,2,15 --- | 1-14,16, 17 |
| P,X | WO 98 33798 A (WARNER LAMBERT COMPANY) 6 August 1998 cited in the application see claims 1-3,9,20,21,26-36 --- -/- | 1-4,14, 17 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

10 June 1999

Date of mailing of the international search report

18. 06. 99

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hartrampf, G

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/22809

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | GEWALD K. ET AL.: "4-Amino-thiazole" JOURNAL FÜR PRAKTISCHE CHEMIE, vol. 35, no. 4, 1967, pages 97-104, XP002095703 cited in the application see compounds VIa and VIb --- | 1-13,16 |
| A | RAJASEKHARAN K.N. ET AL.: "Studies on the synthesis of 5-acyl-2,4-diaminothiazoles from amidinothioureas" SYNTHESIS, vol. 5, 1986, pages 353-355, XP002095704 see compounds 4a-4g and 4i-4m --- | 1-13,16 |
| A | NESTEROV V.N. ET AL.: "Cyclization of nitriles. XXIV. Reactions of cyanamide derivatives of thiocarbamic acids with cyanothioacetamide. Crystal structure of 2-allylamino-4-amino-5-benzoyl-1,3-thiazol e" JOURNAL OF ORGANIC CHEMISTRY, USSR, vol. 24, no. 4, April 1988, pages 762-770, XP002095705 see compounds VI, pages 765 and 769 --- | 1-13,16 |
| A | JENARDANAN G.C. ET AL.: "1-(N-Arylthiocarbamoyl)amidino-3,5-dimeth ylpyrazoles - preparation and use in heterocycle synthesis" SYNTHETIC COMMUNICATIONS, vol. 27, no. 19, 1997, pages 3457-3462, XP002095706 see compounds 5a - 5e, page 3458 --- | 1-13,16 |
| P,A | BINU R. ET AL.: "Synthesis and cyclization of 1-(N-nitroamidino)thioureas to 2,4-diaminothiazoles" ORGANIC PREPARATIONS AND PROCEDURES INTERNATIONAL, vol. 30, no. 1, 1998, pages 93-96, XP002095707 see compounds 4a - 4h, page 94 ----- | 1-13,16 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/22809

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 15
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. ☒ Claims Nos.: 1-14, 16, 17
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-12, 13 (partially), 14

Compounds of formula (I) wherein R2 is a carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic, ring structure having a substituent at the position adjacent to the point of attachment and pharmaceutical compositions containing them

2. Claims: 13 (partially), 16, 17

Compounds of formula (I) wherein R1 is a certain benzenesulfonamide group and R2 is a substituted or unsubstituted carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic, ring structure and pharmaceutical compositions containing them

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 219

Claims Nos.: 1-14,16,17

The claims contain the expression "pharmaceutically active metabolite" which is considered to be a functional feature and renders the scope of the claims ambiguous. Due to such a definition the compounds of formula (I) encompass too broad a range of different chemical groups, not supported by any examples in the descriptive part of the application. Thus claims 1 to 14, 16 and 17 are considered to be insufficiently substantiated by the description, cf. Article 6 PCT. The vast number of theoretically conceivable compounds resulting from claims drafted in such an ambiguous way precludes a comprehensive search. Thus the search should not be considered to cover any pharmaceutically active metabolites of the compounds of formula (I).

A further ambiguity arises since some of the examples, see e.g. compounds A(1) - A(4), A(8), A(12), B, C(1) - C(3), C(6), C(18), C(30), C(31), D(1), D(2), D(4), I(6) - I(17) and I(19) - I(23) are obviously not covered by the present claims. Although explicitly made and tested for inhibitory activity of cyclin-dependent kinases, they do neither contain the mandatory ortho-substitution of radical R₂ (see claim 1 to 12, 13 and 14), nor the benzenesulfonamide moiety for radical R₁ (see claims 13, 16 and 17) which otherwise could be considered to be the distinguishing feature in comparison to the prior art.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/22809

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| WO 9220642 A | 26-11-1992 | AT 159009 T | 15-10-1997 |
| | | AU 658646 B | 27-04-1995 |
| | | AU 1993492 A | 30-12-1992 |
| | | CA 2102780 A | 11-11-1992 |
| | | DE 69222637 D | 13-11-1997 |
| | | DE 69222637 T | 26-02-1998 |
| | | DK 584222 T | 23-02-1998 |
| | | EP 0584222 A | 02-03-1994 |
| | | ES 2108120 T | 16-12-1997 |
| | | GR 3024955 T | 30-01-1998 |
| | | JP 6507643 T | 01-09-1994 |
| | | MX 9202181 A | 01-05-1993 |
| | | US 5409930 A | 25-04-1995 |
| | | US 5480883 A | 02-01-1996 |
| | | US 5710158 A | 20-01-1998 |
| | | US 5795889 A | 18-08-1998 |
| | | US 5646153 A | 08-07-1997 |
| | | US 5721237 A | 24-02-1998 |
| | | US 5714493 A | 03-02-1998 |
| WO 9515758 A | 15-06-1995 | US 5480883 A | 02-01-1996 |
| | | US 5710158 A | 20-01-1998 |
| | | AU 1305095 A | 27-06-1995 |
| | | EP 0871448 A | 21-10-1998 |
| | | SG 54172 A | 16-11-1998 |
| | | US 5795889 A | 18-08-1998 |
| | | US 5646153 A | 08-07-1997 |
| | | US 5721237 A | 24-02-1998 |
| | | US 5714493 A | 03-02-1998 |
| WO 9639145 A | 12-12-1996 | US 5721237 A | 24-02-1998 |
| | | AU 696456 B | 10-09-1998 |
| | | AU 6104496 A | 24-12-1996 |
| | | CA 2223016 A | 12-12-1996 |
| | | CZ 9703503 A | 18-03-1998 |
| | | EP 0831831 A | 01-04-1998 |
| | | SI 9620092 A | 31-08-1998 |
| | | SK 166397 A | 03-06-1998 |
| WO 9833798 A | 06-08-1998 | AU 6648098 A | 25-08-1998 |